REMARKS

Introductory Comments:

Claims 1-85 were examined in the Office Action under reply and stand rejected under (1) 35 U.S.C. 35 U.S.C. §112, second paragraph; (2) the judicially created doctrine of obviousness-type double patenting over U.S. Patent No. 6,274,323; (3) 35 U.S.C. §102(e); and (4) 35 U.S.C. §103(a). These rejections are believed to be overcome for reasons discussed below.

Overview of the Above Amendments:

Claims 86-89 have been canceled as directed to a non-elected invention.

Claims 3, 30-32, 39, 40, 43, 44 and 67 have been amended to recite the subject invention with greater particularity. Specifically, the claims have been amended to delete terminology objected to by the Examiner, to correct dependency, and to provide proper antecedent basis. Support for the amendments can be found in the claims as filed, as well as throughout the specification at, e.g., page 23, lines 27-28.

Amendment of claims 3, 30-32, 39, 40, 43, 44 and 67 and cancellation of claims 86-89 is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants reserve the right to bring the canceled claims again in a related application.

Rejections Under 35 U.S.C. §112, Second Paragraph:

Claims 3, 4, 6-37, 39, 40, 64 and 67 were rejected under 35 U.S.C. §112, second paragraph as indefinite as detailed below.

(1) The Office objected to the terminology "optionally" in the Markush group of claim 3. This term has been eliminated. Thus, this basis for rejection no longer applies.

(2) The Office alleged the use of the terms second, third and fourth microsphere in claims 30-32, respectively, was unclear, as these terms would be understood to mean a different microsphere. Claims 30-32 have been amended to clarify that the microsphere

recited in the first clause is either the same microsphere, or a different microsphere. Accordingly, this basis for rejection has been overcome.

(3) The Office argued that the third and fourth capture probe recited in claims 39 and 40, respectively, lacked antecedent basis. Claims 39 and 40 have been amended to correct dependency. Thus, proper antecedent basis is now provided and this basis for rejection has been overcome.

(4) The Office alleged the term "the five 3' nucleotides" in claim 64 lacked proper antecedent basis. Claim 64 ultimately depends from claim 43. Claim 43 has been amended to recite that the first primer comprises a 3' end of "one to five nucleotides." Thus, this basis for rejection has been overcome and withdrawal thereof is respectfully requested.

(5) The Office alleged that the term "flanking primer" in claim 67 lacked antecedent basis. Claim 67 now depends from claim 66 which recites the presence of a flanking primer. Thus, this basis for rejection has been overcome and withdrawal of the rejection is respectfully requested.

The Obviousness-type Double Patenting Rejection:

Claims 1-85 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-40 of U.S. Patent No. 6,274,323 to Bruchez in view of U.S. Patent No. 6,083,763 to Balch. Applicants request this rejection be held in abeyance until allowable subject matter is indicated in the present application. Applicants will then consider the propriety of filing a Terminal Disclaimer.

Rejections Under 35 U.S.C. §102(e):

Claims 1-5, 12-15, 21-28, 38-42, 43, 45, 52, 53, 55-62, 68, 70, 72, 74-76 and 80-84 were rejected under 35 U.S.C. §102(e) as anticipated by U.S. Patent No. 6,083,763 to Balch ("Balch"). However, applicants do not agree that Balch anticipates the claimed invention.

Anticipation of a claim under §102 *requires* each and every element set forth in the claim be disclosed in a *single* prior art reference. *Davis v. Loesch*, 27 USPQ2d 1440

(Fed. Cir. 1993). Exclusion of a single claimed element from a prior art reference is enough to negate anticipation by that reference. *Atlas Powder Co. v E.I. du Pont De Nemours & Co.* 224 USPQ 409, 411 (Fed Cir. 1984). Balch fails to disclose all of the claimed elements and therefore does not anticipate applicants' claims.

In particular, as illustrated in Figures 3 and 4, the present invention is quite different from the analysis method described in Balch. Figures 3 and 4 show the preparation of a first primer extension product (first PEP), which is a bifunctional oligonucleotide, containing (1) a target complementary region and (2) a target noncomplementary region (the "template"). As illustrated in Figure 4, the second labeled primer is complementary to the first PEP after extension. The first PEP thus generated serves as the **template** for preparation of the second PEP.

The second PEP may be generated from the second labeled primer *in situ* and contemporaneously with the amplification cycling, or it can be generated in a separate reaction. The extension reaction is allowed to proceed such that the second PEP includes a region complementary to the target noncomplementary region of the first PEP.

The second PEP has two significant elements: (1) the label (illustrated as biotin in Figure 5); and (2) the capture sequence which is used to hybridize to support-bound capture probes (see Figures 8 and 9) and is complementary to the target noncomplementary region of the first PEP. The second PEP corresponds to the **amplification product** being detected and recited in the claims. Balch does not teach such an amplification product. Accordingly, Balch does not anticipate the present invention.

Rejections Under 35 U.S.C. §103(a):

Claims 6-11, 16-20, 29-37, 46-51, 54, 63-67, 69, 71, 73, 77-79 and 85 were rejected under 35 U.S.C. §103(a), as detailed below.

(1) Claims 6-11, 16-20, 29-37, 46-51, 54, 63-65, 69, 71, 73, 77 and 85 were rejected under 35 U.S.C. §103(a) as unpatentable over Balch in view of U.S. Patent No. 6,274,323 to Bruchez ("Bruchez").

(2) Claims 6-10, 16-20, 30-37, 46, 48, 51, 69, 71, 73, 77 and 85 were rejected under 35 U.S.C. §103(a) as unpatentable over Balch in view of U.S. Patent No. 6,207,392 to Weiss ("Weiss").

(3) Claims 29, 47, 54, 63-65, 78 and 79 were rejected under 35 U.S.C. §103(a) as unpatentable over Balch in view of U.S. Patent No. 6,426,197 to Duckworth et al. ("Duckworth").

(4) Claims 66 and 67 were rejected under 35 U.S.C. §103(a) as unpatentable over Balch in view of Duckworth and further in view of U.S. Patent No. 5, 942,394 to Ellis et al. ("Ellis").

Applicants note that none of the independent claims, namely, claims 1, 43, 80 or 81, were subject to the above rejections. All pending claims either directly or ultimately depend from each of these claims. Thus, the above bases for rejection are improper and withdrawal thereof is respectfully requested.

Despite the impropriety of the above rejections, applicants submit that the claims are patentable over each of the stated combinations. With respect to rejection (1) above, Bruchez is not properly citable art against the present claims. In particular, Bruchez falls under the provisions of 35 U.S.C. §103(c) as Bruchez's filing date is less than one year prior to the effective filing date of the present application and the subject matter of Bruchez as well as the invention claimed herein were, at the time the invention was made, owned by Quantum Dot Corporation or subject to an obligation to assign to Quantum Dot Corporation. Accordingly, since Bruchez is only citable art under one or more of subsections (e), (f), and (g) of section 102, Bruchez cannot be used to preclude patentability under 35 U.S.C. §103(a). Thus, the combination fails and this basis for rejection should be withdrawn.

Moreover, each of the rejections above relies on Balch as the primary reference. However Balch, in combination with the various secondary and tertiary references recited, fails to render the present claims obvious. It is well settled that for purposes of 35 U.S.C. §103, the differences between the prior art and the claims are not determined based on whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. MPEP §2141.02 citing

Stratoflex, Inc. v. Seroquip Corp., 218 USPQ 871 (Fed. Cir. 1983) and *Schenck v. Northon Corp.*, 218 USPQ 698 (Fed. Cir. 1983) (emphasis in the original). Additionally, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found in either the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992). Further, the fact that references can be combined or modified or that the claimed invention is well within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); *Ex parte Levengood*, 28 USPQ2d 1300 (BPAI 1993).

Applicants respectfully submit that the invention as a whole is not obvious and that there is no suggestion to combine the teachings of the art as asserted. In particular, as explained above, Balch fails to teach or suggest the use of an amplification product with a label and a capture sequence used to hybridize to support-bound capture probes. None of Weiss, Duckworth or Ellis teaches or suggests this critical element that is missing from Balch. Hence, a *prima facie* case of obviousness has not been established and this basis for rejection should be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims define an invention that is patentable over the art and that complies with the requirements of 35 U.S.C. §112. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

If the Examiner notes any further matters which he believes may be resolved by a telephone interview, he is encouraged to contact the undersigned by telephone at 650-843-5589.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 86-89 have been canceled.

Claims 3, 30-32, 39, 40, 43, 44 and 67 have been amended as follows:

3. (Amended) The method of claim 2, wherein the substrate is selected from the group consisting of a microsphere, a chip, a slide, a multiwell plate, a membrane, an optical fiber, and [an optionally] a porous gel matrix.

30. (Amended) The method of claim 6, wherein the sample is suspected of containing a second amplification product from a second target polynucleotide and is further contacted under a second set of hybridization conditions with a second capture probe conjugated to a [second] microsphere,

wherein the second capture probe is a polynucleotide,

wherein the [second] microsphere can be the first microsphere or a different second microsphere,

wherein when the [second] microsphere is a different second microsphere it comprises a second spectral code comprising second fluorescence characteristics, said second spectral code distinguishable from the first spectral code,

wherein the second set of hybridization conditions can be the same as or different than the first set of hybridization conditions,

wherein the second capture probe can hybridize to the second amplification product under the second set of hybridization conditions,

wherein the second amplification product comprises a second label, which can be the first label when the [second] microsphere is a different second microsphere or can be a different second label, and

determining if the second label is associated with the [second] microsphere.

31. (Amended) The method of claim 30, wherein the sample is suspected of containing a third amplification product from a third target polynucleotide and is further contacted under a third set of hybridization conditions with a third capture probe conjugated to a [third] microsphere,

wherein the third capture probe is a polynucleotide,

wherein the [third] microsphere can be the first microsphere, the second microsphere or a different third microsphere,

wherein when the [third] microsphere is a different third microsphere it comprises a third spectral code comprising third fluorescence characteristics, said third spectral code distinguishable from the first spectral code and the second spectral code,

wherein the third set of hybridization conditions can be the first set of hybridization conditions, the second set of hybridization conditions, or a different third set of hybridization conditions,

wherein the third capture probe can hybridize to the third amplification product under the third set of hybridization conditions,

wherein the third amplification product comprises a third label, which can be the first label or the second label when the [third] microsphere is a different third microsphere or can be a different third label, and

determining if the third label is associated with the [third] microsphere.

32. (Amended) The method of claim 31, wherein the sample is suspected of containing a fourth amplification product from a fourth target polynucleotide and is further contacted under a fourth set of hybridization conditions with a fourth capture probe conjugated to a [fourth] microsphere,

wherein the fourth capture probe is a polynucleotide,

wherein the [fourth] microsphere can be the first microsphere, the second microsphere, the third microsphere or a different fourth microsphere,

wherein when the [fourth] microsphere is a different fourth microsphere it comprises a fourth spectral code comprising fourth fluorescence characteristics, said

fourth spectral code distinguishable from the first spectral code, the second spectral code and the third spectral code,

wherein the fourth set of hybridization conditions can be the first set of hybridization conditions, the second set of hybridization conditions, the third set of hybridization conditions or a different fourth set of hybridization conditions,

wherein the fourth capture probe can hybridize to the fourth amplification product under the fourth set of hybridization conditions,

wherein the fourth amplification product comprises a fourth label, which can be the first label, the second label or the third label when the [fourth] microsphere is a different fourth microsphere or can be a different fourth label, and

determining if the fourth label is associated with the [fourth] microsphere.

39. (Amended) The method of claim [1] 38, wherein the substrate is further conjugated to a third capture probe, wherein the third capture probe can preferentially bind to a third capture sequence on a third amplification product, said third amplification product comprising a third label that can be the same as or different than the first label and/or the second label, wherein the binding of the third amplification product to the third capture probe can be independently determined.

40. (Amended) The method of claim [1] 39, wherein the substrate is further conjugated to a fourth capture probe, wherein the fourth capture probe can preferentially bind to a fourth capture sequence on a fourth amplification product, said fourth amplification product comprising a fourth label that can be the same as or different than the first label and/or the second label and/or the third label, wherein the binding the fourth amplification product to the fourth capture probe can be independently determined.

43. (Amended) A method of forming an amplification product detection complex for assaying a sample for a first target polynucleotide, comprising:

providing a first primer and a second primer;

said first primer comprising a 3' end of one to five nucleotides, a first target complementary region that is complementary to the first target polynucleotide, said first target complementary region located at the 3' end of the first primer, and a first target noncomplementary region that is not complementary to the first target polynucleotide at a position 3' of a sequence to which the first target complementary region can hybridize;

said second primer comprising a 3' end and a first label;

providing the sample, said sample suspected of containing the first target polynucleotide;

contacting the sample with the first primer under conditions in which the first target complementary region can hybridize to the first target polynucleotide and the first primer can be extended to form a first primer extension product;

altering the sample conditions to allow dissociation of the first primer extension product from the first target polynucleotide;

wherein the 3' end of the second primer is complementary to the first primer extension product at a position in the first primer extension product that is 3' to the first target complementary region;

contacting the sample with the second primer under conditions in which the second primer can hybridize to the first primer extension product and be extended to form a second primer extension product comprising a first capture sequence that is the complement of the first target noncomplementary region and does not exist elsewhere in the second primer extension product, wherein the second primer extension product is the amplification product;

altering the sample conditions to allow dissociation of the second primer extension product from the first primer extension product; and

contacting the sample with a first capture probe conjugated to a first substrate, wherein the contacting takes place under conditions in which the first capture probe can bind to the first capture sequence of the second primer extension product to form an amplification product detection complex.

44. (Amended) A method [of assaying for an amplification product from a first target polynucleotide comprising performing the method of] according to claim 43, further comprising [and] determining if the first label is associated with the first substrate.

67. The method of claim [63] 66, wherein the flanking primer has a lower melting point for hybridization to the first target polynucleotide than the first primer.